

Guideline-recommended medical therapy for *de novo* heart failure with reduced ejection fraction: be patient waiting for reverse remodelling

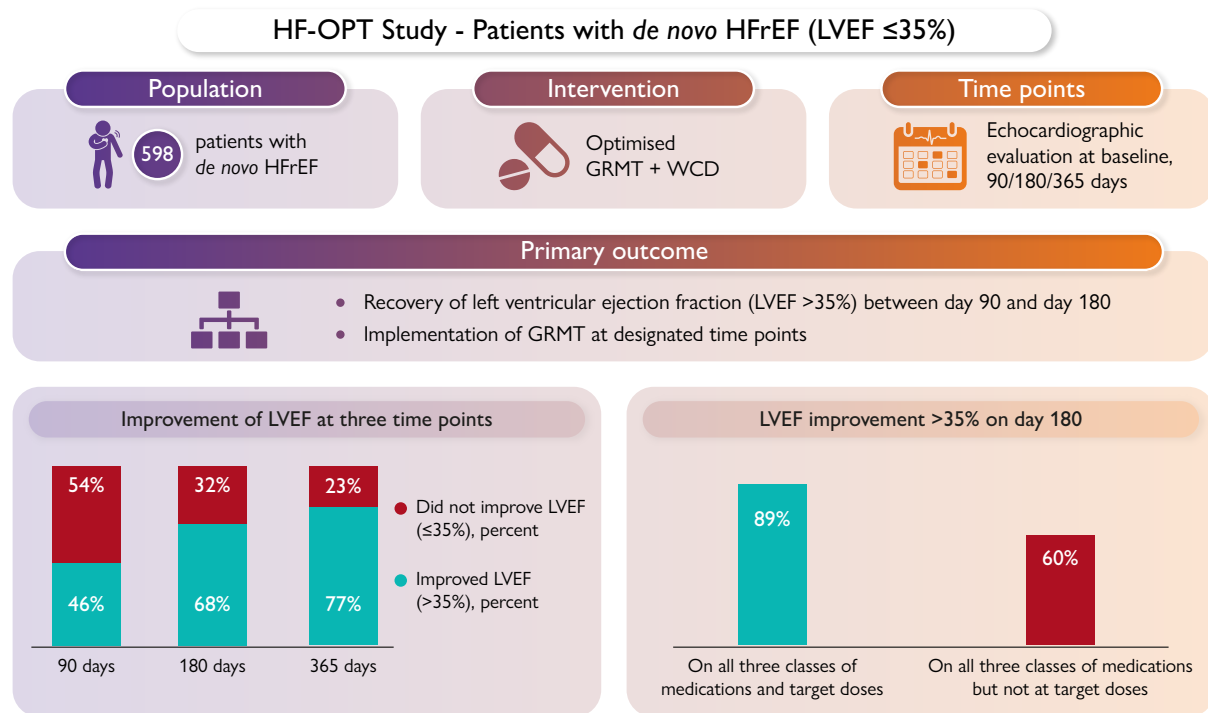
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This editorial refers to ‘Therapy duration and improvement of ventricular function in *de novo* heart failure: the HF-OPT study’, by C. Veltmann *et al.*, <https://doi.org/10.1093/eurheartj/ehae334>.

Graphical Abstract



Some of the main findings obtained in the HF-OPT study

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Guideline-recommended medical therapy (GRMT) for heart failure with reduced ejection fraction (HFrEF) is robustly endorsed by relevant international guidelines and includes angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor–neprilysin inhibitors (ARNIs), beta-blockers, mineralocorticoid receptor antagonists (MRAs), and sodium-glucose co-transporter-2 (SGLT2) inhibitors.^{1–3} Foundational therapy for HFrEF should be initiated promptly and early within the first 4 weeks following the index HF episode and titrated to target doses in a rapid sequence rather than through a conventional stepwise strategy.⁴ Such an approach allows for the simultaneous targeting of multiple pathophysiological pathways detrimental in HF and affords early protection for these patients during the ‘vulnerable phase’ period after hospitalization for HF.⁵ During this time, patients with HFrEF face a substantially elevated risk of adverse events and hospital readmissions.⁶

Pathways that are activated in the failing heart lead, in the long term, to unfavourable structural changes such as cardiomyocyte hypertrophy, fibrosis, chamber dilatation, and molecular and cellular level disturbances.⁷ Simultaneous initiation of GRMT achieves synergistic effects that promote ‘reverse remodelling’ of the myocardium—a dynamic process that enhances systemic neurohumoral regulation and energy metabolism, reduces cardiomyocyte apoptosis, lowers oxidative stress and inflammation, slows down adverse extracellular matrix remodelling, and, ultimately, positively influences gene expression by, for instance, up-regulating the expression of metalloproteinase tissue inhibitors.⁸

Following the initiation of GRMT and the up-titration to target doses, the recovery of left ventricular ejection fraction (LVEF) is typically evaluated through follow-up transthoracic echocardiography after a minimum of 90 days of continuous treatment. This period of at least 3 months on optimized GRMT is conventionally used to determine whether an implantable cardioverter-defibrillator (ICD) device, with or without biventricular pacing, should be implanted in newly diagnosed HFrEF patients experiencing persistent symptoms with LVEF $\leq 35\%$. This approach is officially endorsed in two European Society of Cardiology (ESC) guidelines: one on ventricular arrhythmias, recommending ICD therapy in patients with coronary artery disease and symptomatic heart failure [New York Heart Association (NYHA) class II–III] and LVEF $\leq 35\%$ despite a minimum of 3 months of optimal GRMT,⁹ while a similar indication is outlined in the latest ESC guidelines on HF, with an additional distinction between ischaemic and non-ischaemic aetiologies of cardiomyopathy.¹ On the other hand, it should be noted that in most trials on HF and ICD use, survival curves with respect to ICD vs. no ICD implantation start to diverge at ~ 24 months or later, thus suggesting that for most patients there should be no urgency in ICD implantation.^{10,11} ICDs are not effective for HF patients with poorly controlled symptoms of HF.¹⁰

The optimal time frame for reassessing LV systolic function among patients newly diagnosed with HFrEF remains unclear and lacks evidence. Given these uncertainties, a pertinent question arises: is the 90-day time frame clinically justified and suitable for modern HF patient care? Does it align with the biology of adverse myocardial remodelling and the capacity of contemporary therapies to achieve reverse remodelling within a defined period? Moreover, is it sufficient to determine whether a patient has improved on optimal GRMT, especially considering the consequential decisions that follow, to paraphrase Shakespeare—‘to implant or not to implant, that is the question’?

A recent study suggests that this period might be too short to allow for LV recovery in a substantial proportion of patients with ischaemic cardiomyopathy and concomitant LV dysfunction.¹² Furthermore, there are significant barriers to full implementation of GRMT in clinical

practice and achieving target doses in a considerable portion of HFrEF patients during this potentially narrow time frame.^{5,13}

Some of these clinical questions are addressed by Veltmann and colleagues, in their study published in this issue of the *European Heart Journal*.¹⁴ The investigators enrolled 1300 patients with new-onset HFrEF from 68 sites mainly in the USA and Germany between 2017 and 2022 in a registry designed to assess the intervention rate with a wearable cardioverter defibrillator (WCD) and recovery in LVEF prior to being considered for an ICD.

Most participants were men (73%), with a median age of 59 years, and a median LVEF of 23%. Most patients at index hospitalization (56.7%) belonged to NYHA class II–III while 42% had ischaemic cardiomyopathy. Prevalence rates of comorbidities such as arterial hypertension, diabetes mellitus, atrial fibrillation/flutter, and chronic kidney disease were 64, 27, 23, and 11%, respectively. Regarding initial treatment coverage, renin–angiotensin–aldosterone system (RAAS) inhibitors were initiated in 92% of patients, beta-blockers in 95%, MRAs in 60%, cardiac glycosides in 6.5%, and ivabradine in 5.2% of cases. No data on cardiac resynchronization therapy (CRT) were available. About a quarter of patients were initially treated with an ARNI, while three-quarters of patients received some form of loop diuretic. It is important to note that SGLT2 inhibitors were not considered standard of care for HFrEF patients at the time when HF-OPT was designed and conducted, and uptake of ARNIs also appeared to be suboptimal. Consequently, it would be reasonable to assume that the potential for reverse remodelling with the full ‘fantastic four’ therapies for HFrEF could be even greater, and LVEF improvement $>35\%$ might be underestimated compared with current standards.

Within 90 days, the WCD recorded a ventricular tachycardia (VT)/ventricular fibrillation (VF) event in 24 patients, but only seven patients had an appropriate intervention; the patient was able to abort shocks on most occasions. This intervention rate is somewhat lower than in the WEARIT-II registry in which 22 of 2000 patients received an appropriate shock.⁷ Twelve patients died within 90 days, although it is unclear if any were sudden, 34 patients were lost to follow-up (some of these might have died), and 22 withdrew consent. The authors are unclear about what happened to a further 198 patients. Within 90 days, LV function had recovered in a substantial proportion of patients ($n = 222$; 46%) and 128 received a device before, or because of, the 90-day evaluation. In the following 90 days, a further six patients died (it is unclear if any were sudden), five had an ICD implanted, 46 were not re-evaluated for a variety of reasons, and 54 had incomplete data, leaving 487 patients who could be re-evaluated at all three time points. Finally, with continuing GRMT, further recovery in LV function was observed, with 77% of patients evaluated at 1 year achieving an LVEF $>35\%$. In numerical terms, LVEF improved from a median of 23% at the index echocardiography to 34% at 90 days and to 40% at 180 days. Those patients ($n = 392$) who continued follow-up to 1 year demonstrated even greater improvement in LVEF, with the median being 44% [interquartile range (IQR) 37–53]. These favourable trends were paralleled by the trend of overall reduction in loop diuretic use and GRMT target dose up-titration across all study time points.

These data collectively convey an important takeaway message: the process of reverse remodelling is not completed in a significant proportion of patients with HFrEF at 90 days, and more time should be allowed for LV recovery estimation and decision to prophylactically implant an ICD device. This can only be achieved through the full implementation, continuation, and rapid up-titration of GRMT for patients with *de novo* HFrEF, as these steps are crucial to unlocking the full potential of reverse remodelling (*Graphical Abstract*). Moreover, if these

processes are implemented quickly, they are more likely to translate into better clinical outcomes.¹⁵

The independent predictors of LVEF improvement beyond 35% in this study were a high initial LVEF, higher blood pressure, a history of cardiac arrest, and a history of atrial fibrillation (AF). Of note, in the cohort of patients whose LVEF improved at 180 days, there was a significantly greater proportion of patients with a history of AF, which is likely to suggest the importance of rhythm or rate control strategies that were used to correct tachyarrhythmia which then translated to improvement of systolic function.

Importantly, data from the present study indicate that the chances of LV recovering to >35% were similar for both ischaemic and non-ischaemic aetiologies of cardiomyopathy. However, a granular analysis of the data reveals a greater proportion of patients with non-ischaemic cardiomyopathy reaching LVEF >50% at 180 and 360 days (24% and 30% vs. 18% and 17%, respectively). There are several potential caveats for this finding that the authors discuss, with a lower degree of ventricular substrate and ischaemic scar burden present in the non-ischaemic vs. ischaemic cohort being one of the more significant ones.

In conclusion, Veltmann and colleagues should be commended for delivering an important study that informs the management of patients with new-onset HFrEF. They illustrated how early initiation and ongoing optimization of GRMT in this patient cohort can lead to the recovery of LV function well beyond the conventional 90-day mark. This discovery could potentially streamline decision-making regarding the implantation of ICDs. Moreover, it is plausible that this effect could be even stronger and occur more rapidly nowadays with the full implementation of the 'fantastic four' medicines. However, this assumption should be rigorously tested in future trials.

Declarations

Disclosure of Interest

The author declares no disclosure of interest for this contribution.

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